B3

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/03837 A1

(51) International Patent Classification[7]: B01L 3/02

(21) International Application Number: PCT/GB00/02678

(22) International Filing Date: 12 July 2000 (12.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9916406.3 13 July 1999 (13.07.1999) GB

(71) Applicants *(for all designated States except US)*: **BIOROBOTICS LIMITED** [GB/GB]; Bennell Court, Comberton, Cambridge CB3 7DS (GB). **CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED** [GB/GB]; The Old Schools, Trinity Lane, Cambridge CB2 1TS (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ELMES, Stuart, Antony** [GB/GB]; BioRobotics Limited, Bennell Court, Comberton, Cambridge CB3 7DS (GB). **MOORE, David, Frank** [GB/GB]; Trinity Hall, Cambridge CB2 1TJ (GB). **PEARSON, Jonathan** [GB/GB]; 4 Babingley Close, Watlington, Norfolk PE33 0TR (GB).

(74) Agents: **DRIVER, Virginia, Rozanne** et al.; Page White & Farrer, 54 Doughty Street, London WC1N 2LS (GB).

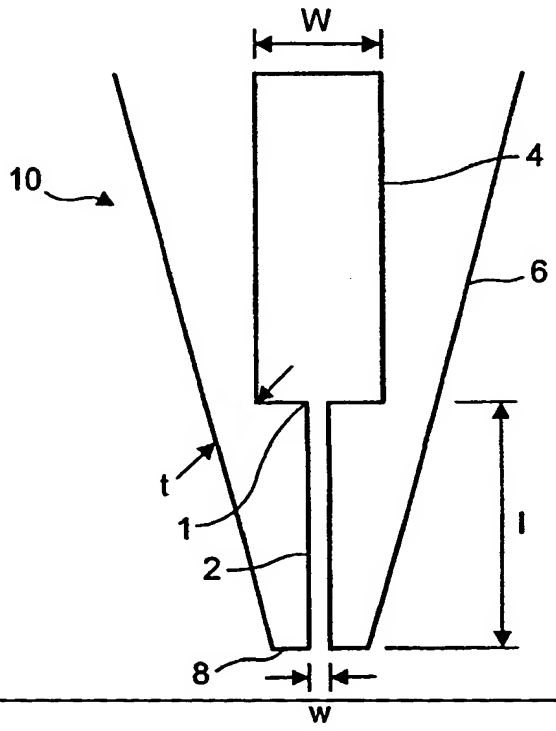
(81) Designated States *(national)*: GB, JP, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LIQUID TRANSFER PIN



(57) Abstract: A method of producing a liquid transfer pin (10) having a tip (8) and defining a slot (1) extending from the tip (8) for transferring one or more drops of a fluid to a substrate, the slot comprising an elongate outlet portion (12) extending from the tip (8) and a reservoir portion (4) connected to a distal end of the outlet portion and having a larger cut-out volume than that of the outlet portion, said method comprising the step of cutting the slot into a tip of a solid pin, wherein the width of the outlet portion at the tip is no more than 20 microns directly after cutting.

WO 01/03837 A1

LIQUID TRANSFER PIN

The present invention relates to a liquid transfer pin for transferring one or more drops of fluid to a substrate, and to a method of producing such a pin, and in particular, to a liquid transfer pin for producing microarrays of droplets for testing in the field of life sciences, and to a method of producing such a liquid transfer pin.

Molecular biologists have a need to be able to create an array of thousands of different fluidic samples on a microscope slide o7r other substrate. Such arrays are typically prepared using a liquid transfer tool. The tip of the liquid transfer tool is dipped into a relatively large volume source of the sample liquid (typically 5 to 40 microlitres) to pick up a droplet on the tip of the tool. The tip of the liquid transfer tool is then contacted with the substrate to transfer the droplet to the substrate. In the case that an array comprising dots of different sample fluids is to be prepared, the above procedure is repeated the necessary times to give the desired number of spots of the first sample fluid; the tool is then cleaned; and then the whole procedure is repeated for each of the plurality of sample fluids.

These liquid transfer tools are typically combined in groups attached to a common base to provide a multi-pin liquid transfer tool so that a plurality of droplets can be transferred to the substrate in a single movement of the base to form an array.

The array-forming process can be further expedited by providing the liquid transfer tool with a reservoir which

is connected to the tip of the liquid transfer tool and which can hold enough of the sample fluid for transferring a plurality of droplets to one or more substrates. The provision of such a reservoir greatly reduces the number of moves the liquid transfer tool needs to make between the substrate(s) and the sample fluid source.

Monolithic liquid transfer tools prepared by the micro-machining of solid pins are known. A slot extending from the tip of the pin is cut into the pin using wire electronic discharge machining (EDM). The smallest slots that have been produced with this technology are slots having a width in the range of 30 to 40 microns.

There has however been a demand for a liquid transfer tool having smaller slot widths for creating an array of droplets of yet smaller diameter in order to create an array of yet greater droplet density. This demand has been somewhat met by modifying the monolithic liquid transfer pins mentioned above by plastic deformation of the tip of the pin to reduce the width of the slot at the tip of the pin from the machined width of 30 to 40 microns to a smaller width.

Such plastic deformation has generally been carried out in the following ways with reference to Figures 7(a), 7(b), 8(a) and 8(b) of the accompanying drawings. According to one approach, the pin is machined with the aim of producing a perfect point as shown in Figure 7(a). The pin is then deformed in the manner generally shown in Figure 7(b) when the tip of the pin is first tapped on the substrate. This method is particularly uncontrolled

and results in some pins which become deformed to the extent that they no longer work.

According to a another approach, the pin is machined to have an increased tip diameter as shown in Figure 8(a). The pin is then plastically deformed before use by a crimping operation or with a screw arrangement to produce an axially tapered slot having a narrowed exit at the tip.

However, the inventors of the present invention have found that these plastic deformation processes are inherently inconsistent resulting in pins of varying slot widths and tip diameters. As mentioned above, multi-pin liquid transfer tools require a group of liquid transfer pins having uniform dimensions in order to produce an array of uniformly-sized droplets, and a lot of time and effort is therefore required to select pins having matching dimensions.

An aim of the present invention is to provide a liquid transfer pin and a method of producing a liquid transfer pin which at least partially resolves the above-mentioned problems in the prior art.

According to a first aspect there is provided a method of producing a liquid transfer pin having a tip and defining a slot extending from the tip for transferring one or more drops of a fluid to a substrate, the slot comprising an elongate outlet portion extending from the tip and a reservoir portion connected to a distal end of the outlet portion and having a larger cut-out volume than that of the outlet portion, said method comprising the step of producing the pin by a non-deformation process, such as

cutting, wherein the width of the slot at the tip of the pin directly produced by the non-deformation process is no more than 20 microns.

According to a second aspect of the present invention, there is provided a method of producing a liquid transfer pin having a tip and defining a slot extending from the tip for transferring one or more drops of a fluid to a substrate, the slot comprising an elongate outlet portion extending from the tip and a reservoir portion connected to a distal end of the outlet portion and having a larger cut-out volume than that of the outlet portion, said method comprising the step of cutting the slot into a tip of a solid pin, wherein the width of the outlet portion at the tip is no more than 20 microns directly after cutting.

According to a third aspect of the present invention, there is provided a method of producing a liquid transfer pin having a tip and defining a slot extending from the tip for transferring one or more drops of a fluid from the tip to a substrate, the slot comprising an elongate outlet portion extending from the tip and a reservoir portion connected to a distal end of the outlet portion and having a larger cut-out volume than that of the outlet portion, said method comprising using copper vapour laser cutting to form the slot in a tip of a solid pin.

According to a fourth aspect of the present invention there is provided a liquid transfer pin produced by any of the above-described methods.

According to a fifth aspect of the present invention there is provided a liquid transfer pin for transferring one or more drops of a fluid to a substrate from a tip thereof, the liquid transfer pin defining a slot extending from the tip, wherein the slot comprises an elongate outlet portion extending from the tip, and a reservoir portion connected to a distal end of the outlet portion, the width of the reservoir portion being greater than the width of the outlet portion at the point where it is connected to the outlet portion.

According to a sixth aspect of the present invention, there is provided a liquid transfer pin for transferring one or more drops of a fluid to a substrate from a tip thereof, the liquid transfer pin defining a slot extending from the tip, wherein the slot comprises an outlet portion extending from the tip and having a substantially axially uniform width, and a reservoir portion connected to the distal end of the outlet portion and having a substantially axially uniform width, the width of the outlet portion being less than the width of the reservoir portion.

According to a seventh aspect of the present invention, there is provided a liquid transfer pin for transferring one or more drops of a fluid to a substrate from a tip thereof, the liquid transfer pin defining a slot extending from the tip, wherein the slot comprises an outlet portion extending from the tip and having a substantially axially uniform width of less than 20 microns, and a reservoir portion connected to a distal end of the outlet portion and having a larger capacity than the outlet portion.

According to an eighth aspect of the present invention, there is provided a multi-pin liquid transfer tool comprising a plurality of liquid transfer pins as described above.

According to a ninth aspect of the present invention, there is provided a method of producing a multi-pin liquid transfer tool by attaching a plurality of liquid transfer pins to a common base, each liquid transfer pin having a tip and defining a slot extending from the tip, wherein each liquid transfer pin is produced by cutting a slot into a tip of a solid pin, the width of the slot at the tip being less than 20 microns directly after cutting.

According to an tenth aspect of the present invention, there is provided a method of producing a multi-pin liquid transfer tool by attaching a plurality of liquid transfer pins to a common base, each liquid transfer pin having a tip and defining a slot extending from the tip, wherein each liquid transfer pin is produced by cutting a slot into a tip of a solid pin by copper vapour laser cutting.

According to a eleventh aspect of the present invention, there is provided a multi-pin liquid transfer tool produced by either of the above-described methods.

According to a twelfth aspect of the present invention, there is provided a method of producing an ordered array of spots on a substrate using a liquid transfer pin or a multi-pin liquid transfer tool as described above.

According to a thirteenth aspect of the present invention there is provided a method of transferring one or more drops of liquid to one or more substrates using a liquid transfer pin, wherein the liquid transfer pin has a tip and defines a slot extending from the tip and is produced by cutting a slot into a tip of a solid pin, wherein the width of the slot at the tip is no more than 20 microns directly after cutting.

According to a fourteenth aspect of the present invention, there is provided a method of transferring one or more drops of liquid to one or more substrates using a liquid transfer pin, wherein the liquid transfer pin has a tip and defines a slot extending from the tip and is produced by cutting a slot into a tip of a solid pin by copper vapour laser cutting.

According to a preferred embodiment of the above-described aspects of the present invention, the slot extends right through the pin in a direction perpendicular to the longitudinal axis of the pin. In an alternative embodiment, all or a part of the slot may only extend partially through the pin in a direction generally perpendicular to the longitudinal axis of the pin, i.e. may only be open on one side in a direction perpendicular to the axis of the pin.

Embodiments of the present invention will be described hereunder, by way of example only, with reference to the accompanying drawings, in which:-

Figure 1 shows a schematic cross-sectional view of the working end of a liquid transfer pin according to an embodiment of the present invention;

Figure 2 is a graph showing the performance of liquid transfer pins according to embodiments of the present invention with respect to consistency of volume dispensed;

Figure 3 shows a schematic perspective view of the working end of the liquid transfer pin shown in cross-section in Figure 1; and

Figures 4(a) and 4(b) are shematic cross-sectional views taken through lines A-A and B-B in Figure 3, respectively.

Figures 5(a) and 5(b) are cross-sectional views of the kind shown in Figures 4(a) and 4(b) for an alternative embodiment of the liquid transfer pin according to the present invention.

Figure 6 shows a multi-pin liquid transfer tool according to the present invention.

Figures 7 and 8 schematically show the plastic deformation processes used in the prior art.

Figures 9(a) and 9(b) are schematic cross-sections of an alternative embodiment of a liquid transfer pin according to the present invention, taken perpendicular to the longitudinal axis of the pin.

A liquid transfer pin having the geometry generally shown in Figures 1 and 3 is produced according to the following method. A 5mm diameter solid bar of 17-04ph stainless steel is turned, where necessary, and sharpened at one

end to produce a tapered solid pin having the desired dimensions. Copper vapour laser cutting is then used to cut a slot 1 in the tip of the solid pin 6 which extends from the tip 8 of the pin 6 in a direction substantially parallel to the longitudinal axis of the pin 6. As shown in Figures 3, 4(a) and 4(b), the slot extends right though the pin in a direction perpendicular to the longitudinal axis of the pin 6 (i.e. the direction shown by the arrows in Figures 4(a) and 4(b)).

However, as mentioned above, the present invention is not limited to pins in which the slot extends right through the pin, but includes pins in which the outlet portion and/or the reservoir portion only partially extend through the pin in a direction perpendicular to the longitudinal axis of the pin, i.e. are only open on one side in a direction perpendicular to the longitudinal axis of the pin. Figures 9(a) and 9(b) are schematic cross-sectional views of a liquid transfer pin according to the present invention having a slot comprising an outlet portion 20 and a reservoir portion 22 which only extend partially through the pin in a direction generally perpendicular to the longitudinal axis of the pin. Such an alternative construction can be advantageous in the cases of pins having particularly small tip diameters, since it provides the pin with increased mechanical strength against deformation upon use.

The slot comprises an outlet portion 2 having a substantially axially uniform width and a reservoir portion 4 having a substantially axially uniform width which is larger than that of the outlet portion 2.

The term "substantially axially uniform width" refers to the feature that the width of the respective portion of the slot is substantially uniform along the longitudinal (axial) length of the respective portion of the slot, i.e. from the proximal end to the distal end of the respective portion of the slot.

As shown in the cross-sections shown in Figures 4(a) and 4(b), the slot produced by copper vapour laser cutting has a width which is slightly tapered in a direction generally perpendicular to the axis of the liquid transfer pin, i.e. the direction shown by the arrows in Figures 4(a) and 4(b). In the case of such a slot whose width is not uniform in a direction generally perpendicular to the longitudinal axis of the pin, the term "width" refers to the average width of the respective portion of the slot in the direction shown by the arrows shown in Figures 4(a) and 4(b). As already mentioned above, the average width of the respective portions of the slot is nevertheless substantially uniform along the axial length of the respective portions of the slot, i.e. from the proximal end to the distal end of the respective portions of the slot.

According to an alternative embodiment, the width of the outlet portion and the reservoir portion of the slot are, as shown in Figures 5(a) and 5(b), also uniform in the direction perpendicular to the axis of the pin, i.e. the direction shown by the arrows in Figures 5(a) and 5(b). In this alternative embodiment, the opposing walls of the outlet portion 2 and reservoir portion 4 are thus substantially parallel to each other.

The copper vapour laser cutting is carried out as follows. The solid pin is secured on a mount in the path of the laser beam. The mount is moveable in x and y directions perpendicular to each other and perpendicular to the path of the laser beam. The beam of the laser is focussed down to a dot size of about 5 microns to achieve a sufficient power density to vaporise the material of the solid pin. The laser is then pulsed whilst displacing the pin in the x and y directions by moving the mount to successively vaporise and remove a surface layer of dimensions corresponding to those of the desired slot. This process is repeated to remove successive surface layers until the pin has been cut right through to leave a slot of the desired dimensions in the tip of the pin.

In the case of producing a pin in which the slot only partially extends through the pin in a direction generally perpendicular to the longitudinal axis of the pin, the laser cutting is only continued until a slot of the desired depth has been cut.

One of the advantages of copper vapour laser cutting is that the pulsing can be carried out at a high frequency, whereby a large amount of material can be vaporised and eliminated in a short period of time. This reduces the time required to produce the slot of desired shape.

The geometry of the resulting monolithic liquid transfer pin 10 is generally shown in Figures 1, 3, 4(a) and 4(b). The outlet portion 2 preferably has a width, w of no more than 20 microns, preferably in the range of 10 to 20 microns, and further preferably in the range of 10 to 15 microns; and the reservoir portion preferably has a

width, W in the range of 50 to 300 microns, such as about 100 microns. The length, l of the outlet portion 2 is preferably minimised whilst retaining a sufficient wall thickness "t" to prevent plastic deformation upon use of the liquid transfer pin. It is preferably minimised because it is preferred that the volume of the outlet portion is neglible compared to the volume of the reservoir portion. The length of the reservoir portion is preferably in the range of 300 to 2000 microns, such as about 1000 microns.

The working end of the liquid transfer pin shown in Figures 1 and 3 is smoothly tapered towards the tip. Alternatively, it may be tapered in a step-wise manner or not tapered at all.

Furthermore, as shown in Figures 4 and 5 the liquid transfer pin shown in Figures 1 and 3 has a generally circular cross-sectional symmetry. The tip of the liquid transfer pin is squared off and preferably has a diameter in the range of 50 to 200 microns, such as 100, 150 or 200 microns. However, the present invention is not limited to liquid transfer pins having a circular cross-sectional symmetry, and the present invention may be applied to pins having non-circular cross-sectional symmetry such as a tapered or non-tapered thin blade-shaped pin having a generally rectangular cross-section.

Since the resultant liquid transfer pin has the required small dimensions without having to subject the liquid transfer pin to subsequent plastic deformation, liquid transfer pins produced according to this method have consistent dimensions. This consistency means that the liquid transfer pin of the present invention is

particularly useful for producing a multi-pin liquid transfer tool as schematically shown in Figure 6 to be used for simultaneously creating an array of a large number of small droplets of uniform size. In Figure 6, a plurality of liquid transfer pins 10 having working ends as shown in Figures 1 and 3 are orderly arranged on a common base 12, such that the tips of the plurality of liquid transfer pins lie in a single horizontal plane.

The liquid transfer pin of the present invention is used in the conventional manner. The liquid transfer pin is dipped into a source of the sample fluid whereby the outlet portion and reservoir portions become at least partially filled with the sample fluid. The tip of the liquid transfer pin is then tapped against the substrate on which the array is to be formed by relative movement of the tip of the pin towards the substrate to transfer a droplet of the sample fluid from the tip of the liquid transfer pin to the substrate. The tip of the liquid transfer pin is then repeatedly tapped at different portions of the surface of the substrate to form an ordered array of spots on the surface of the substrate.

The liquid transfer pin generally shown in Figures 1 and 3 exhibits excellent performance with respect to consistency of droplet volume with increasing spot number, as shown in the graph in Figure 2. The intensity given on the y-axis is directly proportional to the volume of the droplet dispensed on the substrate. As can be seen from the graph, the volume dispensed is substantially consistent until the very last few spots with a very sharp reduction in dispensed volume for those last few spots. This is in contrast to conventional liquid transfer pins in which the tail-off is much

shallower whereby the dispensed volume is consistent for a smaller proportion of the total number of spots.

CLAIMS

1. A method of producing a liquid transfer pin having a tip and defining a slot extending from the tip for transferring one or more drops of a fluid to a substrate, the slot comprising an elongate outlet portion extending from the tip and a reservoir portion connected to a distal end of the outlet portion and having a larger cut-out volume than that of the outlet portion, said method comprising the step of cutting the slot into a tip of a solid pin, wherein the width of the outlet portion at the tip is no more than 20 microns directly after cutting.

2. A method of producing a liquid transfer pin according to claim 1 wherein the width of the slot at the tip is between 10 and 20 microns directly after cutting.

3. A method of producing a liquid transfer pin according to claim 1 or claim 2 wherein the outlet portion of the slot has a substantially axially uniform width.

4. A method of producing a liquid transfer pin according to claim 3 wherein the reservoir portion of the slot has a substantially axially uniform width larger than that of the outlet portion.

5. A method of producing a liquid transfer pin according to claim 1 wherein the liquid transfer pin is at least partially tapered towards the tip.

6. A method of producing a liquid transfer pin according to any preceding claim wherein the cutting is copper vapour laser cutting.

7. A method of producing a liquid transfer pin having a tip and defining a slot extending from the tip for transferring one or more drops of a fluid from the tip to a substrate, the slot comprising an elongate outlet portion extending from the tip and a reservoir portion connected to a distal end of the outlet portion and having a larger cut-out volume than that of the outlet portion, said method comprising using copper vapour laser cutting to form the slot in a tip of a solid tapered pin.

8. A method according to claim 7 wherein the width of the slot at the tip is no more than 20 microns.

9. A method according to claim 8 wherein the width of the slot at the tip is in the range of 10 to 20 microns.

10. A method according to any one of claims 7 to 9 wherein the elongate outlet portion has a substantially axially uniform width.

11. A method according to claim 10 wherein the reservoir portion has a substantially axially uniform width larger than that of the outlet portion.

12. A method according to claim 7 wherein the liquid transfer pin is at least partially tapered towards the tip.

13. A method according to claim 7 wherein the tip of the liquid transfer pin has a circular cross-section with a diameter in the range of 50 to 200 microns.

14. A liquid transfer pin produced by a method according to any of claims 1 to 13.

15. A liquid transfer pin for transferring one or more drops of a fluid to a substrate from a tip thereof, the liquid transfer pin defining a slot extending from the tip, wherein the slot comprises an elongate outlet portion extending from the tip, and a reservoir portion connected to a distal end of the outlet portion, the width of the reservoir portion being greater than the width of the outlet portion at the point where it is connected to the outlet portion.

16. A liquid transfer pin according to claim 15 wherein the width of the outlet portion at the tip is no more than 20 microns.

17. A liquid transfer pin according to claim 16 wherein the width of the outlet portion at the tip is in the range of 10 to 20 microns.

18. A liquid transfer pin according to any of claims 15 to 17 wherein the outlet portion has a substantially axially uniform width.

19. A liquid transfer pin according to any of claims 15 to 18 wherein the reservoir portion has a substantially axially uniform width.

20. A liquid transfer pin for transferring one or more drops of a fluid to a substrate from a tip thereof, the liquid transfer pin defining a slot extending from the tip, wherein the slot comprises an outlet portion extending from the tip and having a substantially axially uniform width, and a reservoir portion connected to a distal end of the outlet portion and having a substantially axially uniform width, the width of the outlet portion being less than the width of the reservoir portion.

21. A liquid transfer pin according to claim 20 wherein the width of the outlet portion is no more than 20 microns.

22. A liquid transfer pin according to claim 21 wherein the width of the outlet portion is in the range of 10 to 20 microns.

23. A liquid transfer pin for transferring one or more drops of a fluid to a substrate from a tip thereof, the liquid transfer pin defining a slot extending from the tip, wherein the slot comprises an outlet portion having a substantially axially uniform width of less than 20 microns, and a reservoir portion connected to a distal end of the outlet portion and having a larger capacity than the outlet portion.

24. A liquid transfer pin according to claim 23 wherein the width of the outlet portion is in the range of 10 to 20 microns.

25. A liquid transfer pin according to claim 24 wherein the reservoir portion also has a substantially axially uniform width.

26. A multi-pin liquid transfer tool comprising a plurality of liquid transfer pins according to any of claims 14 to 25 attached to a common base.

27. A method of producing a multi-pin liquid transfer tool by attaching a plurality of liquid transfer pins to a common base, each liquid transfer pin having a tip and defining a slot extending from the tip, wherein each liquid transfer pin is produced by cutting a slot into a tip of a solid pin, the width of the slot at the tip being less than 20 microns directly after cutting.

28. A method of producing a multi-pin liquid transfer tool by attaching a plurality of liquid transfer pins to a common base, each liquid transfer pin having a tip and defining a slot extending from the tip, wherein each liquid transfer pin is produced by cutting a slot into a tip of a solid pin by copper vapour laser cutting.

29. A multi-pin liquid transfer tool produced by the method defined in claim 27 or claim 28.

30. A method of producing an ordered array of spots on a substrate using a liquid transfer pin according to any one of claims 15 to 25 or a multi-pin liquid transfer tool according to claim 26 or claim 29.

31. A method of producing an ordered array of spots according to claim 30 wherein the diameter of the spots is in the range of 50 to 200 microns.

32. A method of transferring one or more drops of liquid to one or more substrates using a liquid transfer pin, wherein the liquid transfer pin has a tip and defines a slot extending from the tip and is produced by cutting a slot into a tip of a solid pin, wherein the width of the slot at the tip is no more than 20 microns directly after cutting.

33. A method of transferring one or more drops of liquid to one or more substrates using a liquid transfer pin, wherein the liquid transfer pin has a tip and defines a slot extending from the tip and is produced by cutting a slot into a tip of a solid pin by copper vapour laser cutting.

34. A liquid transfer pin substantially as hereinbefore described with reference to any of Figures 1 and 3 to 5 of the accompanying drawings.

35. A multi-pin liquid transfer tool substantially as hereinbefore described with reference to Figure 6 and any of Figures 1 and 3 to 5 of the accompanying drawings.

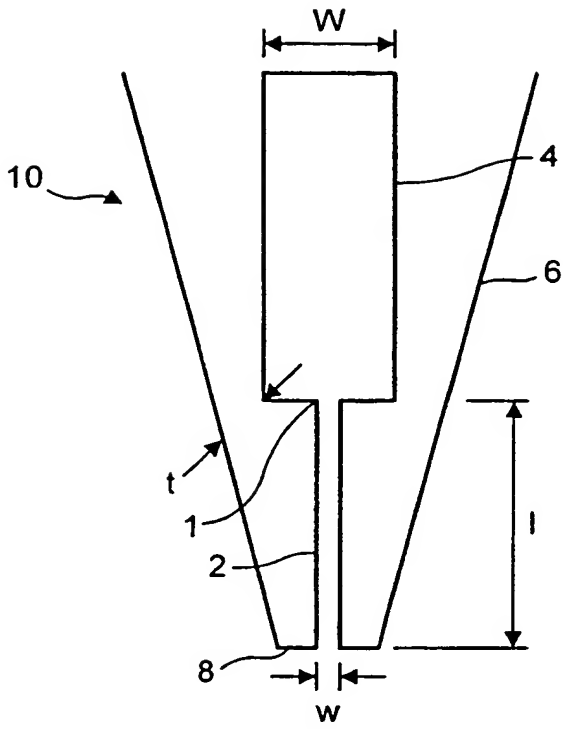

W
10
4
6
t
1
2
l
8
w

FIG. 1

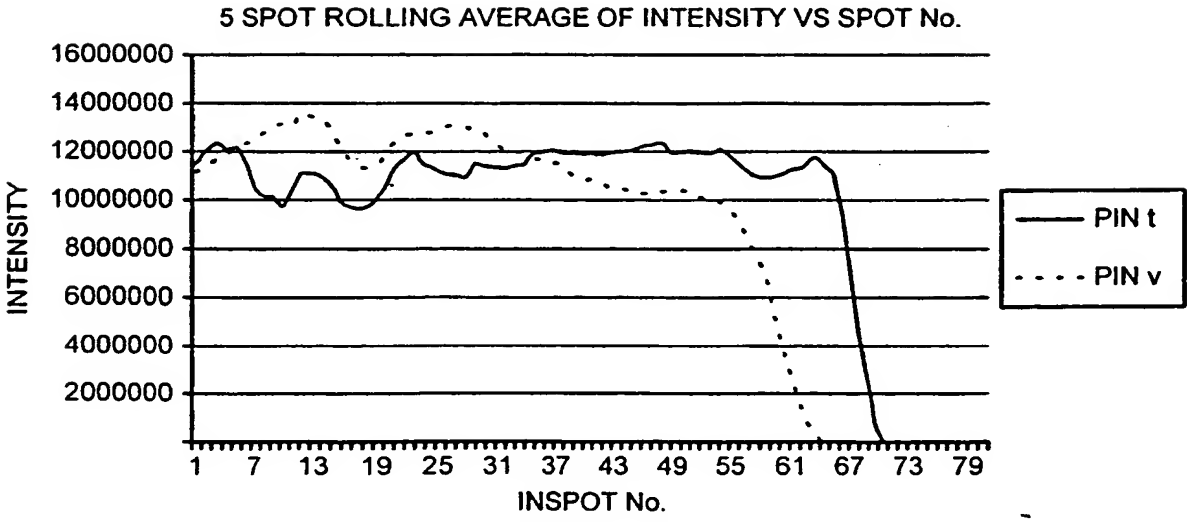

5 SPOT ROLLING AVERAGE OF INTENSITY VS SPOT No.
16000000
14000000
12000000
10000000
8000000
6000000
4000000
2000000
INTENSITY
1 7 13 19 25 31 37 43 49 55 61 67 73 79
INSPOT No.
PIN t
PIN v

FIG. 2

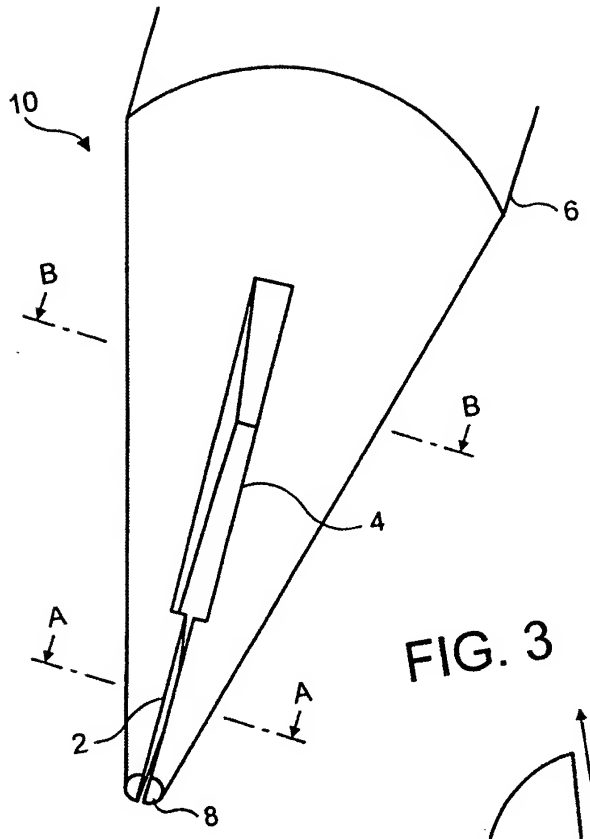


FIG. 3

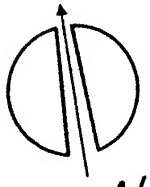


FIG. 4(a)

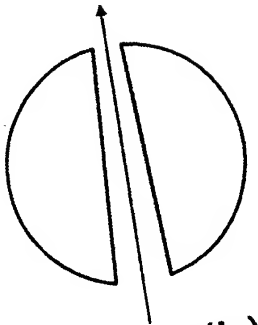


FIG. 4(b)

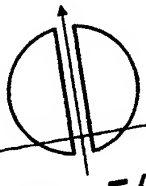


FIG. 5(a)

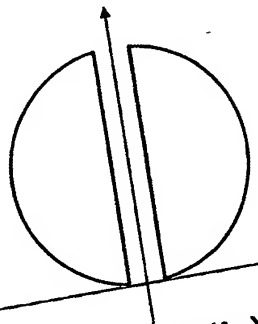


FIG. 5(b)

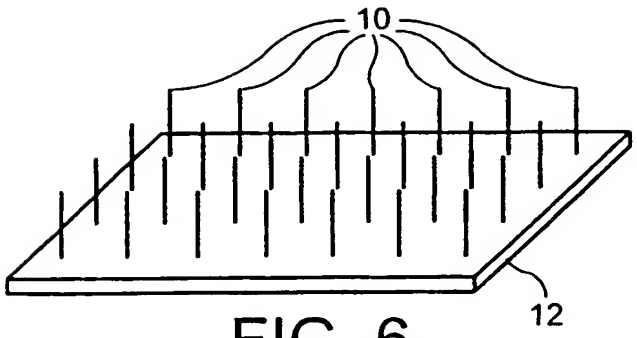


FIG. 6

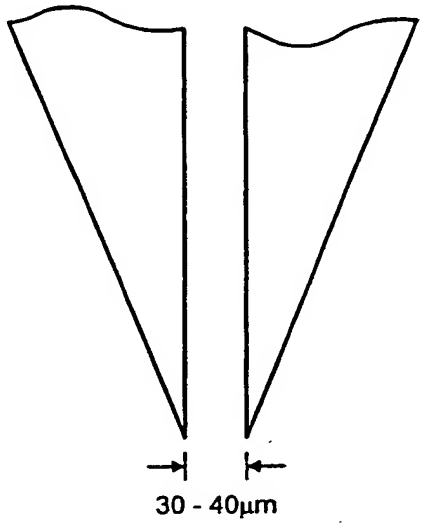


FIG. 7(a)

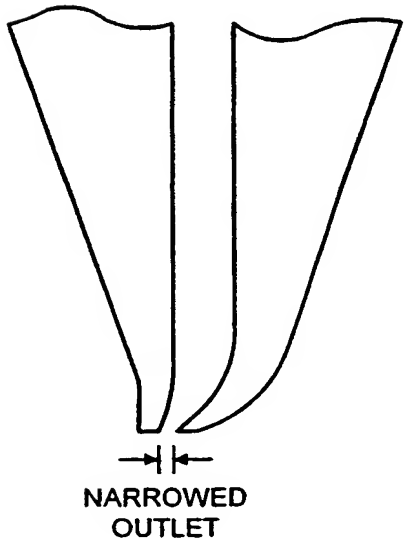


FIG. 7(b)

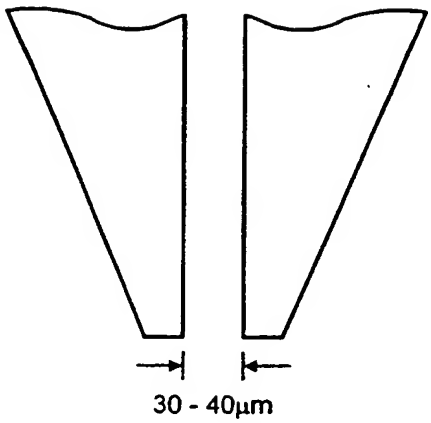


FIG. 8(a)

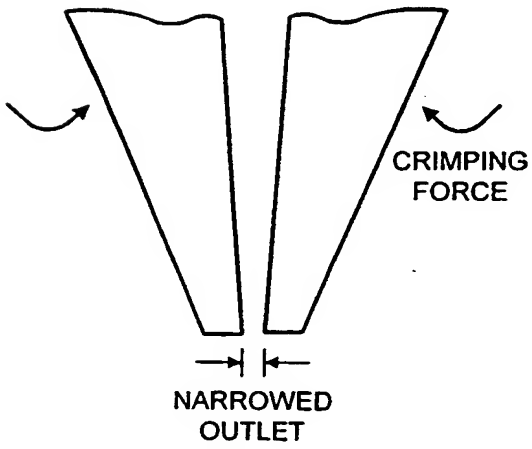


FIG. 8(b)

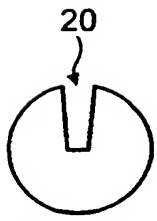


FIG. 9(a)

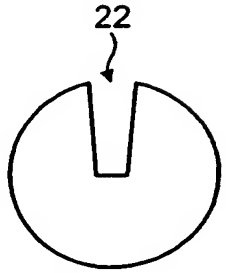


FIG. 9(b)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02678

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01L G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	US 6 101 946 A (MARTINSKY RICHARD S) 15 August 2000 (2000-08-15) abstract; figures 2-4,6,7 column 3, line 13 -column 3, line 41 column 4, line 24 -column 5, line 44 column 6, line 45 -column 6, line 67	1-33
P,A	WO 00 25923 A (DAVIES MARTIN CLEMENT ;ELMES STUART ANTONY (GB); MILNE WILLIAM IRE) 11 May 2000 (2000-05-11) abstract; figures 8,10,11 page 1, line 1 -page 1, line 18 page 5, line 9 -page 5, line 16 page 7, line 8 -page 7, line 28	1,7,14, 15,20, 23, 26-30, 32,33

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2000	17/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Runser, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 00/02678

C.(Continuation) DOCUMENTS CONSIDERED T BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 770 151 A (ROACH DAVID J ET AL) 23 June 1998 (1998-06-23) abstract; figures 2-6 column 4, line 5 -column 5, line 50	1-33
A	WO 99 31468 A (FEYGIN ILYA ;PHARMACOPEIA INC (US)) 24 June 1999 (1999-06-24) abstract; figures 1-8 page 4, line 17 -page 8, line 11	1-33
A	US 5 807 522 A (BROWN PATRICK O ET AL) 15 September 1998 (1998-09-15) abstract; figures 1-3 column 7, line 17 -column 9, line 62	1-33
P,A	WO 00 01798 A (CARTESIAN TECHNOLOGIES INC) 13 January 2000 (2000-01-13) abstract; figures 1-3 page 5, line 28 -page 9, line 30	1-33
A	US 3 616 387 A (SIEBERT CHRISTOPHER J ET AL) 26 October 1971 (1971-10-26) abstract; figures 6,7 column 4, line 41 -column 5, line 8	1,7,14, 15,20, 23, 26-30, 32,33

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...nal Application No
PCT/GB 00/02678

Patent document cited in search report	Publication date	Patent family member(s)	Publication dat
US 6101946 A	15-08-2000	NONE	
WO 0025923 A	11-05-2000	NONE	
US 5770151 A	23-06-1998	EP 0991472 A	12-04-2000
		WO 9746319 A	11-12-1997
WO 9931468 A	24-06-1999	US 5957167 A	28-09-1999
		AU 1923299 A	05-07-1999
		US 6116297 A	12-09-2000
US 5807522 A	15-09-1998	AT 180570 T	15-06-1999
		AU 709276 B	26-08-1999
		AU 2862995 A	15-01-1996
		CA 2192095 A	28-12-1995
		DE 69509925 D	01-07-1999
		DE 69509925 T	09-12-1999
		EP 0804731 A	05-11-1997
		EP 0913485 A	06-05-1999
		ES 2134481 T	01-10-1999
		GR 3030430 T	30-09-1999
		JP 10503841 T	07-04-1998
		US 6110426 A	29-08-2000
		WO 9535505 A	28-12-1995
WO 0001798 A	13-01-2000	AU 4861099 A	24-01-2000
US 3616387 A	26-10-1971	DE 2055948 A	19-05-1971
		FR 2071887 A	17-09-1971
		GB 1333926 A	17-10-1973